ABSTRACTS

This section of the ANNALS is published in collaboration with the two abstracting Journals, ABSTRACTS OF WORLD MEDICINE, and OPHTHALMIC LITERATURE, published by the British Medical Association.

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section “ACTH, Cortisone, and other Steroids” includes abstracts and titles of articles dealing with steroid research which, although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and modus operandi of steroid therapy.

Acute Rheumatism


The results of administration of corticotrophin (ACTH) for short periods (average 7 days) to 28 patients with active rheumatic carditis are reported from New York Hospital. As judged by the clinical findings and the results of fluoroscopic examination the attack was quickly arrested in 24 cases in which the eosinophil count was maintained below 10 per c.mm. (treatment considered “adequate”). In four of eight cases in which the eosinophil count rose above 10 per c.mm. (treatment considered “inadequate”), there was a recurrence of symptoms after treatment was discontinued. The arrest of the carditis was more prompt and complete when treatment was begun within 10 days of the onset of the attack; when treatment was started later there was no reversal of cardiac enlargement. During the follow-up period three patients had recurrent attacks; this incidence, the authors point out, is no greater than might be expected. In the authors’ view these observations indicate that short-term ACTH therapy is followed by arrest and termination of active carditis, and that it favourably alters the natural course of the disease. 


As a measure of adrenocortical function the author determined the eosinopenic response in a small series of children aged between 7 and 13 years admitted to the Children’s Hospital, Melbourne, suffering “from the major manifestations of rheumatic fever, including chorea”. The response was estimated in four groups tested respectively with 10 mg. ACTH intramuscularly, 0-3 mg. adrenaline subcutaneously, and 60 and 30 mg. ephedrine sulphate given by mouth. Except for those receiving the smaller dose of ephedrine sulphate, all patients showed a significant fall in the eosinophil count after 4 hours. Control observations were made on the previous day, and the timing was arranged to obviate normal diurnal variations.

The author concludes that no evidence is given by this method of examination to suggest any hypofunction of the adrenal cortex or interference with the pituitary-adrenocortical relationship in rheumatic fever. The study was made with a view to substantiating “the presumed allergic reactions in rheumatic fever” based on the belief that ACTH and cortisone inhibit the delayed type of allergic reaction. As a secondary observation it was noted that the normal level of circulating eosinophil cells in this group was somewhat higher than the upper limit of the normal defined by Discombe (Lancet, 1946, 1, 195).

Harry Coke.


At the Children’s Memorial Hospital, Montreal, the effect of administration of cortisone on the incidence of heart disease was studied in 100 patients with active rheumatic fever, eighty similar patients who had no cortisone serving as controls. The patients in both groups were between 3 and 14 years of age. The majority of the treated group received 200 mg. cortisone for 2 days and 100 to 150 mg. daily for 28 days or longer. The degree of cardiac involvement was assessed from the results of clinical, electrocardiographic, and fluoroscopic examination.

There was no significant difference between the two groups in the incidence of heart disease. The authors state that the lower death rate in the treated group was not statistically significant, but that in view of the dramatic improvement in many severely ill patients it appeared possible that the death rate from acute rheumatic fever was reduced by the drug. 

Oswald Savage.


Of 638 children admitted to the Children’s Heart Hospital, Philadelphia, with rheumatic fever during the
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10-year period 1940-50, 467 were subsequently given various forms of sulphonamide prophylaxis for periods ranging from 3 months to 2 years. During the first 3 years of the period treatment was given only between September 1 and June 1 each year, the dosage ranging from 3 to 6 g. daily to maintain a serum level of 4 to 5 mg. per 100 ml. During the next 7 years treatment was given continuously throughout the year, but the dose used was smaller, varying from 0·5 to 1·0 g. daily. All these children were in hospital while the prophylactic treatment was being given. Only two recurrences occurred in children taking sulphonamides, compared with nine recurrences among 44 control patients. No recurrences among 154 patients in a 2-year period before the introduction of prophylactic sulphonamide. In 34 additional cases the patient started taking prophylactic sulphonamide but developed toxic manifestations (chiefly rashes, haematological reactions, and albuminuria) which made it necessary to discontinue the drug. The incidence of toxic manifestations was unrelated to the dosage used.

In view of the toxic complications of sulphonamide prophylaxis, penicillin prophylaxis was substituted in 1950, and up to July 1, 1952, 102 children had been treated, each receiving 100,000 units crystalline benzyl penicillin twice daily by mouth in liquid form. None of these children had a recurrence of rheumatic activity, and none had toxic reactions. R. S. Illingworth.

Serum Diphenylamine Reaction in Rheumatic Fever.

It has been reported (Niazí and State, Cancer Res., 1948, 8, 653) that the patient’s serum in several disease states contains increased levels of a substance giving a purple colour with diphenylamine. This reaction is measured by the intensity of the colour reaction of serum added to the diphenylamine reagent. At the Rheumatic Fever Research Institute (Northwestern University), Chicago, raised values were obtained with serum from patients in the acute stage of rheumatic fever, while serum from patients who had recently recovered and others who had shown no signs of activity for one year gave normal values. The intensity of this colour reaction and the erythrocyte sedimentation rate showed close parallelism. The substance in the serum reacting with diphenylamine is unknown, but the authors claim that connective tissue is a rich source of the substance, and that its concentration in the blood is related to the intensity of the inflammatory process.

[Yet another empirical test is added to the already existing battery of tests, with no proof of its superiority over any of the older methods of assessment of activity in rheumatic fever.]

G. Loewi.


Patients with rheumatic fever in a U.S. Army hospital and varying in age from 18 to 38 years were given 1·6 g. enteric-coated sodium salicylate every 4 hours, together with one of the following adjuvant drugs: sodium bicarbonate, magnesium trisilicate, aluminium hydroxide gel, aluminium hydroxide tablets. Blood samples for salicylate determination were taken at 8 a.m. every second day.

In 24 patients receiving enteric-coated sodium salicylate alone, an average plasma salicylate level of 42·2 mg./100 ml. (range 33·4 to 57·0 mg./100 ml.) was found. In a further sixteen patients, the administration of 1·6 g. sodium bicarbonate with their salicylate depressed the plasma salicylate level, the average reading being 29·8 mg./100 ml. (range 24·9 to 37·0 mg.). Several of these patients complained of bloating and gaseous eructations. The average plasma salicylate level in seventeen patients receiving 0·65 g. sodium bicarbonate with each dose of salicylate was 35·9 mg./100 ml. (range 26·7 to 48·6 mg.); there were few complaints of gastric upset. In thirteen patients receiving 1·0 g. magnesium trisilicate with each dose of salicylate, the levels ranged from 38·8 to 54·2 mg./100 ml. (average 43·0 mg.); some patients given the higher concentrations suffered from dyspnoea, nervousness, and anorexia. The figures in nine patients receiving aluminium hydroxide in tablet form were: average 46·5 mg./100 ml.; range 40·0 to 54·0 mg. In this group nervous irritability accompanying the higher salicylate levels was prominent. Of the sixteen patients started on aluminium hydroxide gel, 8 to 16 ml. for each dose of salicylate, five became so nauseated that they could not continue. The average plasma salicylate level of the remaining eleven patients in this group was 49·8 mg./100 ml. (range 42·8 to 59·2 mg.).

Sodium bicarbonate was found to have the effect of restoring toward normal the diminished carbon dioxide combining power resulting from salicylate therapy. Magnesium trisilicate and aluminium hydroxide gel and tablets were as effective as sodium bicarbonate in relieving gastric distress, but did not lower the plasma salicylate level or raise the carbon dioxide combining power. Incidental observations were the apparent lack of effect of salicylate on the elevated erythrocyte sedimentation rate and the prolonged P-R interval, and the absence of any haemorrhagic manifestations. Norval Taylor.

The author reports his results in 35 children with acute rheumatism treated with aureomycin. Of these, 27 were observed for a period of 2 years, and are divided into three groups according to the progress made: (1) four children, three relapsed because treatment was too short, having lasted only 6, 5, and 10 days respectively, and the dosage was too low (0·5, 5, and 6 g.). The fourth patient suffered a recrudescence of the acute rheumatic process, with decompensated mitral stenosis 6 months after cessation of treatment, but became symptomless after a 12-day course of aureomycin (total dose 8 g.).
(2) six patients, treatment was begun in three children, 4, 28, and 14 days after the onset of the attack, and lasted
16, 23, and 15 days, the dosage being 8, 16, and 16 g. In these three all clinical signs disappeared without any other antirheumatic treatment; the electrocardiogram, which had shown a myocardial change in the child in whom treatment had been started only after 28 days, returned to normal after 23 days. In the other three the erythrocyte sedimentation rate became normal after 11, 12, and 7 days of treatment with total doses of 12, 12, and 16 g. All six children were in good health 4 months after cessation of treatment.

(3) Seventeen children, no further attack occurred for 10 to 24 months, in spite of recurrent tonsillitis or infectious disease. Restrictions of activities or school attendance was imposed on only two patients with compensated mitral stenosis; tonsillectomy was performed in three children. In seven cases treated 4 to 14 days (average 8) after the onset of the first attack, the cardiac findings were normal; in four patients treated 7 to 21 days (average 11) after the onset, mild cardiac involvement was observed; in six cases in which treatment with aureomycin was delayed up to 12 months after a repeated attack, severe mitral and aortic valvular disease was found. Nevertheless, in all cases the electrocardiogram was within normal limits at the time of follow-up examination.

The gain in weight amounted from 2·1 to 10 kg. (average 4·3), with a rapid weight increase of 7 to 10 kg. during prepuberty and puberty. Dental caries was found in ten cases of the last group. The blood picture was normal in all children, and there was no complaint of joint or muscle pain. The author advises the continuation of treatment with aureomycin for a maximum of 28 days, with full dosage for 21 days. The effective dose seems to be 40 to 50 mg./kg. body weight per day. Vitamin B or nicotinic acid was simultaneously given to all the children, and additional vitamin K to some of them. The degree of residual cardiac damage seemed to depend upon the time lag between the onset of the disease and beginning treatment. Nevertheless, even cases with severe cardiac involvement resistant to other antirheumatic therapy, responded well. The treatment was well tolerated even in younger children. It is stressed, however, that aureomycin treatment cannot replace the therapeutic measures indicated in cases of disturbed circulation. In hyperactive cases with recurrent relapses, repeated small transfusions with blood from women in the 4th to 6th month of pregnancy are advised. M. Dynski-Klein.

ANNALS OF THE RHEUMATIC DISEASES


The pathogenesis of chorea has been studied by Russian workers on the basis of Pavlov's theories, the symptoms being attributed to cerebral excitation (and subsequent inhibition) caused by cerebral oedema. Investigations carried out at the Saratov Medical Institute have further shown that this oedema affects especially the subcortical centres and that it is part of a general disturbance of water metabolism.

With the aim of causing dehydration and thus reducing cerebral oedema, two methods of treatment have been used in cases of chorea.

(1) "Combined osmotherapy", consisting of intramuscular injections of 5 to 10 ml. of 25 per cent. magnesium sulphate solution (the dose being diminished with clinical improvement) and repeated lumbar puncture. Of 21 patients so treated, four were cured after 18 days and eleven after 19 days; the remaining six show some degree of improvement.

(2) A course of six to twelve injections of a mercurial diuretic given at 3-day intervals. Of 27 patients treated in this way, thirteen were cured after 19 days and eleven were improved; the condition of two others was unchanged and in one it became worse.

In both groups, 1 to 3 g. of sodium salicylate was given daily in addition. W. Szaynok.


Histological study at the Peter Bent Brigham and Boston City Hospitals of 183 auricular appendages, out of a total of 223 removed at operation from patients thought to be free of active carditis, showed the presence of Aschoff bodies in 83 (45 per cent.), these bodies being numerous (up to 10 or 12) in 21 cases (11·5 per cent.). They were located in the endocardium or, more commonly, in the loose-structured subendocardium; none were found in the myocardium proper. Of 172 appendages examined the endocardial thrombosis was present in 71 (41 per cent.). but in these cases the incidence of Aschoff bodies was low. In six of the 22 cases coming to necropsy and showing Aschoff bodies, it was found that when these lesions were frequent in the left auricular appendage, they were also frequent in the left ventricular myocardium and vice versa.

A. C. Lendrum.


**Pathogenesis of Transitory Disturbances of Conduction in the Heart in Acute Rheumatism.** (Rilievi nella patogenesi dei disturbi transitori di eccitocaduzione cardica in corso di reumatismo acuto focale.) FRANCESCONI, M., and BOVO, G. (1953). Folia cardiol. (Milano), 12, 311. 7 fgs, 31 refs.


**Experience with Gantrisin as a Prophylactic Measure in Rheumatic Fever, with special reference to the Ability of Children to tolerate the Drug over a Prolonged Period.** KURTZ, C. M. (1953). J. Urol. (Baltimore), 70, 802.
Chronic Articular Rheumatism (Rheumatoid Arthritis)


This study was made on 44 patients suffering from chronic rheumatoid arthritis of long standing who were showing signs of deterioration. The investigation was conducted by three separate groups of the two drugs being tested, namely, p-aminobenzoic acid and acetylsalicylic acid, some patients received doses of cortisone, "rarely exceeding 25 mg. per day", and three patients were given physiotherapy. Potassium p-aminobenzoate was given in six 2-g. doses per day, and 0-6 g. acetylsalicylic acid was given four times a day.

It is claimed that 34 of the patients were improved but that 3 months elapsed from the beginning of treatment until the improvement became apparent. This was characterized by a decrease in joint pain, heat, swelling, and tenderness, and in nodule size, and increased freedom of movement, with loss of fever and gain in weight [but no detailed results are given].

[This report indicates that treatment with a combination of the drugs named may be of some value. However, the manner in which this trial was conducted does not allow definite conclusions to be drawn.]

G. Loewi.


The literature on the use of thiacetazone ("thiosemicarbazone") in the treatment of tuberculosis and rheumatoid arthritis is reviewed. Heilmeyer found that administration of thiacetazone in rheumatoid arthritis was followed by a rapid fall in the erythrocyte sedimentation rate (E.S.R.), with a remission in joint symptoms. He suggested that the drug had a cortisone-like effect which it exerted by blocking mineral corticoids and increasing the action of glucocorticoids. The object of the present investigation, which was carried out at the Kivelä Hospital, Helsinki, was twofold:

1) to determine the effect of thiacetazone in rheumatoid arthritis;

2) to determine whether this drug acted synergistically with cortisone—for example, by exerting a toxic effect on the liver and delaying cortisone metabolism.

A daily dose of 0-2 to 0-3 g. thiacetazone was given for an average of 80 days to 37 patients suffering from rheumatoid arthritis, four of them receiving both thiacetazone and cortisone. Although considerable improvement was observed, in 26 of the 37 this was transient, relapse following when administration of the drug ceased. The E.S.R. fell markedly in most of the patients but rose again when treatment was discontinued. Toxic reactions, noted in 25 patients, consisted in nausea and vomiting, skin rash, granulocytopenia, albuminuria, and urobilinuria; in five cases treatment had to be stopped because of severe nausea. It was found that toxic reactions were closely related to the size of the dose, none being observed when the dose of thiacetazone was less than 0-2 g. daily. No evidence of a synergistic action was found in the four patients who received both thiacetazone and cortisone.

The authors conclude that the transient effect of thiacetazone and the serious toxic reactions render this drug of little value in the treatment of rheumatoid arthritis. [There was no control investigation.]

W. Tegner.


It is pointed out that the results of prolonged treatment of rheumatoid arthritis with cortisone and ACTH leave much to be desired. Though there is good functional improvement the degree of improvement in terms of rheumatoid activity is usually Grade 2 (major) or Grade 3 (minor), rarely Grade 1 (complete remission).

The author, from New York Medical College, describes his experiences with a gold preparation, aurothioglycanide ("Lauron"), in the treatment of 69 patients over a period of 8 years. If the disease was recent in onset and not very active, 25 mg. was given; this dose was always given initially if the patient had had toxic effects from gold therapy previously. The majority of patients received 50 mg. initially, this initial dose being given once a week for 3 weeks. If no improvement or toxic effects occurred the dose was then doubled, and again increased, if necessary, at 8 or 10 weeks; it never exceeded 150 mg. weekly. This dosage level was continued until improvement was well established, but if after 6 months there was no improvement, treatment was discontinued. In one group of patients who improved, treatment was discontinued, while in another, a maintenance dose of 50 to 150 mg. at 2- or 4-weekly intervals was given. The total duration of therapy varied between 5 weeks and 3 years.

Altogether 26 patients, regardless of the stage of the disease, showed improvement with the initial phase of treatment. When patients with early arthritis (Stage 1 or Stage 2) were considered, it was found that in just over one-half there was complete remission or major improvement. This initial response was further enhanced by maintenance therapy, since in fifteen out of seventeen there was a satisfactory end-result.

A comparison of the incidence of toxic effects and their severity with those observed in a series of patients receiving aurothioglucose in another clinic suggested that aurothioglycanide was less toxic.

C. E. Quin.


In continuation of the study reported by Copeman and others (Brit. med. J., 1952, 1, 397), the authors now give further details of 17-ketosteroid excretion after
cortisone administration, and also report changes after ACTH therapy. A new method of analysing the non-ketonic fraction has revealed changes not previously reported. The work was carried out at the Middlesex Hospital Medical School, London. Urine was collected from normal male and female subjects, and from patients with rheumatoid arthritis before and during treatment with ACTH and cortisone. The benzene extract of the urine hydrolysate was fractionated by the usual methods and final fractions (ketonic alcohols, ketonic non-alcohols, non-ketonic 3α-alcohols and non-ketonic 3β-alcohols) were assayed chromatographically. The non-ketonic fractions were assayed by conversion of the alcohols to 3:5-dinitrobenzoates (Kellie and others, Biochem. J., 1953, 53, 578).

Comparison of the steroid excretion in the normal subjects and in untreated arthritic patients showed that:

1. The androsterone: androsterone ratio is higher in the latter, a change already reported in at least one other pathological condition;
2. The non-ketonic alcohols are unchanged;
3. The non-ketonic 3α-alcohols (probably mono-, di-, and tri-hydroxy alcohols) are considerably reduced in quantity;
4. The amount of non-ketonic 3β-alcohols excreted in both normal and rheumatoid arthritic subjects was negligible.

A close study was made of three arthritic patients who were receiving hormone therapy: ACTH, cortisone, and ACTH followed by cortisone. The administration of ACTH led to a great increase in steroid excretion, which was reflected in all fractions but was mainly due to increased output of androsterone and aetiocholanolone. Treatment with cortisone was followed by an irregular small rise in 17-ketosteroids excretion, mainly in the ketonic alcohols and particularly aetiocholanolone; it is pointed out that this finding is contrary to that of other workers.

Nancy Gough.

**Investigation of Combined Treatment with ACTH and ascorbic acid in rheumatoid arthritis.** [In English. Dalgaard, O. Z. (1953). Acta endocr. (Kbh.), 13, 39. 10 figs, 16 refs.]

In view of various reports of the favourable effect of using para-aminobenzoic acid (PABA) as an adjuvant to cortisone in the treatment of rheumatoid arthritis, the authors set out to determine whether a combination of PABA and ACTH (corticotron) had a similar synergistic or additive effect, and whether PABA alone influenced hormone production by the adrenal cortex. Accordingly, five patients suffering from rheumatoid arthritis of long standing were treated at the Kommunehospitalet, Copenhagen, with PABA and small doses of ACTH. They were first given 10 mg. of ACTH and 12 g. of PABA daily for 5 days; then, after a 5-day interval, they received 10 mg. of ACTH daily for 5 days without PABA, and finally, after a further 5-day interval, the first course was repeated. The effect of treatment was assessed from clinical appearances and by determination of the eosinophil count and urinary 17-ketosteroid excretion.

The administration of these small doses of ACTH produced some slow symptomatic improvement in four of the five patients treated, with a rise in urinary 17-ketosteroid excretion and a fall in eosinophil count, during the treatment periods, but the addition of PABA appeared to make no difference to the response.

A second group of five patients suffering from other diseases were given 12 g. of PABA daily for 5 days, the urinary 17-ketosteroid excretion being determined daily. The drug had no demonstrable effect.

G. Loewi.

**Treatment of Rheumatoid Arthritis with Hypoglycaemia.**


At Roskilde County and Municipal Hospital, Denmark, fifteen cases of rheumatoid arthritis were treated by the induction of hypoglycaemia with insulin. Each morning for 4 weeks the fasting patient was given sufficient insulin to produce hypoglycaemic symptoms, a carbohydrate meal being given at the end of 3 hours unless the severity of the symptoms necessitated administration of glucose at an earlier stage. The status of patients was assessed on appearance and performance of joints and on the erythrocyte sedimentation rate before, during, and after the course of treatment. A great improvement was noted in four cases, slight improvement in six, and no improvement in five immediately after the course. At a follow-up examination 4 to 9 months later, however, there was a great improvement in one case, slight improvement in four, and none in ten.

B. Nordine.


The authors recall that Long and others (Lancet, 1951, 1, 1085) postulated that, on the analogy of the diminution of experimental tuberculin hypersensitivity in guinea-pigs by cortisone and ACTH, other factors influencing such sensitivity might also influence arthritis in man. They also suggested that the action of ACTH and cortisone is mediated through ascorbic acid, and the effect of this substance was therefore tried in patients with arthritis, as were the effects of glucose-1-phosphate and lysergic acid diethylamide, both of which modify experimental tuberculin sensitivity.

For the tests carried out at St. Mary’s Hospital, London, ten patients with rheumatoid arthritis and one patient with polyarteritis nodosa with predominant involvement of the joints were chosen. They were kept on a scorbutic diet and all were given acetylsalicylic acid, 30 to 60 gr. (2 to 4 g.) daily, and codeine when required. In one patient, the scorbutogenic diet improved the arthritis, but this improvement continued when ascorbic acid was administered, and cortisone and ACTH produced further improvement while the patient was still on this diet. Two other patients experienced no change in their symptoms, while tuberculin sensitivity increased in one patient, but decreased when ACTH was given. In four patients receiving glucose-1-phosphate and in a further...
four given lysergic acid diethylamide, no effect on the arthritis or tuberculin sensitivity could be detected.

It is clear that no evidence was found to support an analogy between experimental tuberculin sensitivity and the tissue reactions in rheumatoid arthritis. The possibility is suggested that the tuberculin reaction in the guinea-pig and in man may differ.  

G. Loewi.


β-Tetrahydronaphthylamine is primarily a sympathetic stimulant with some action on the parasympathetic system. During an investigation of its action on the vegetative nervous system, carried out in the Medical Clinic of the University of Münster, it was noticed that individuals suffering from rheumatoid arthritis were able to move the affected joints more easily and with less pain after being given the drug. The possible analgesic properties of the drug were then tested by determining its effect on the strength of electric stimulus necessary to elicit pain when applied to the region of the median nerve at the wrist. The experiment showed that the drug had no effect on sensitivity to pain in rheumatic and non-rheumatic subjects alike. Another possible mode of action was suggested by the observation that muscle tone appeared to be decreased after administration of the drug, non-rheumatic subjects complaining that their limbs felt heavy and useless, although movements could be carried out with an effort. Patients with rheumatoid arthritis, on the other hand, were very impressed by their increased activity and lack of pain. As a working hypothesis, therefore, it was assumed that the drug caused muscular relaxation and a loosening of the capsules of affected joints, relief of pain following automatically. No effect of the drug on the electrical reactions of muscles could be demonstrated electromyographically, but investigation of its effect on intramuscular tension by the technique of Henderson (including measurement of the resistance to intramuscular injection of saline) in eighteen patients with rheumatoid arthritis showed that a definite reduction of tension occurred on injection of β-tetrahydronaphthylamine in all fifteen cases in which the drug also relieved joint pain. In one case a fall of tension was unaccompanied by relief of pain, but this was attributed to bony ankylosis; in the remaining two cases there was no fall in tension and no relief of pain.

It is suggested that the drug should be used as a therapeutic agent in its own right. There is, in fact, evidence that the initially effective dose of 0.025 g. has to be doubled after 7 days. Its main value would appear to be in facilitating active and passive movement of the affected joints, particularly when supplies of cortisone are not available. In 28 cases (22 women, 6 men) of rheumatoid arthritis the drug was given half an hour before physiotherapy (in 20 cases subcutaneously and in 8 by mouth). The results were "excellent" in fifteen and "good" in eleven; no toxic effects were observed.

D. Preiskel.


The author briefly reviews the literature dealing with "Atebrin" (mepacrine), and recalls the claim made by Freedman and Bach that the drug may be of value in the treatment of rheumatoid arthritis. In the series here reported, seventeen female and seven male patients suffering from active rheumatoid arthritis were treated with 0.1 g. Atebrin three times daily for one week and then with 0.1 g. twice a day as a maintenance dose. In two of these patients the activity of the rheumatoid arthritis ceased completely after 8 weeks' treatment. In all the other patients signs of activity remained after periods of treatment of up to 12 weeks, but seven were subjectively improved, and eleven showed slight improvement. There were no serious toxic reactions, but yellowing of the skin usually appeared in the second week of treatment. Four detailed case histories are given.

The author concludes that Atebrin has some anti-rheumatic action, but that this action is sufficiently efficacious in only about one-third of the patients treated. The series reported was uncontrolled.

W. Tegner.


It has been shown, both experimentally in animals and in the human subject, that hypophysectomy results in atrophy of the spleen and, conversely, that splenectomy leads to hypertrophy of the anterior pituitary gland. The author of this paper considers Felty's syndrome to be a variant of rheumatoid arthritis, and has observed a hyperplastic marrow associated with agranulocytopenia or leucopenia in affected cases. He presents detailed reports of three cases of Felty's syndrome in which splenectomy was performed at the Rochester General Hospital, New York. In two of these there was marked improvement, not only in the blood picture but also in the arthritic condition, following operation. In the third case similar improvement followed splenectomy, but leukaemia developed 3 years later. Short reports are also given of three further patients who developed Felty's syndrome but had been treated with cortisone or corticotrophin. In one case, although both the splenomegaly and the leucopenia disappeared during cortisone treatment, they returned 4 weeks after its cessation. In the remaining two cases, splenomegaly developed after cortisone and corticotrophin therapy respectively. In these cases treatment with the hormones led to a temporary improvement in the blood picture and a diminution in size of the spleen, but did not prevent the development of splenomegaly or result in permanent reversal of splenomegaly if already present.

Splenectomy appears to be the treatment of choice in cases of Felty's syndrome, and it is suggested that one effect of removal of the spleen may be to bring about hypertrophy of the anterior lobe of the pituitary and thus increase the natural supply of corticotrophin.

R. E. Tunbridge.
Some Observations on Anaemia in Rheumatoid Arthritis.


The nature of the anaemia in rheumatoid arthritis was studied at the Royal National Hospital for Rheumatic Diseases, Bath, in a varying number of active cases of the disease, with special regard to changes in the peripheral blood and bone marrow, blood, plasma, and corpuscle volumes, and alterations in iron metabolism. Estimations of blood values were made on one hundred cases or more, and the anaemia was found to be predominantly normochromic or hypochromic in type, the reduction in haemoglobin value and erythrocyte count being greater in the more active cases. Blood values bore no relationship to the duration of the disease or the age of the patient, and did not reveal any haemodilution.

A study of reticulocytes, faecal urobilinogen, and plasma bilirubin on fourteen, nineteen, and twelve cases respectively revealed no significant abnormality, except in one case in which these values were raised. Sternal marrow smears showed no major abnormality, but there was a slight tendency to hypercellularity, arrest of maturation, and delayed haemoglobinisation of the normoblasts. The iron-binding capacity of the plasma was in most cases within normal limits, but estimation of the serum iron level and intestinal iron-absorption capacity revealed evidence of defective iron assimilation. A small proportion of cases which were refractory to iron given by mouth showed improvement of the anaemia when iron was given intravenously, but the response was not always complete.

Mary D. Smith.


The results of administration of cortisone and ACTH in fifteen cases of Still's disease are reported. In spite of a high dosage and a long period of treatment side-effects were fewer than expected. The typical moon-face was common, but there was no electrolyte disturbance or significant glycosuria. Of the fifteen patients three died and two were lost to subsequent follow-up. The condition was well controlled by cortisone in one patient and partially controlled in two. One other patient had limitation of movement, although the disease was quiescent, and six were well at the time of reporting.

The authors conclude that administration of ACTH or cortisone modifies the signs and symptoms of Still's disease more consistently than any other form of treatment, and that while the outcome in this series is not significantly better than that observed by other workers before these drugs were available, it may prove to be better in time. Oswald Savage.


The authors made detailed inquiries into the family history in 224 cases of rheumatoid arthritis collected from private practice and a number of clinics and hospitals in Cleveland, Ohio. Similar inquiries were made in a control series of 488 patients, all free from rheumatoid arthritis, although 122 had Heberden's nodes, 59 ankylosing spondylitis, and 47 gout.

The incidence of rheumatoid arthritis among 1,443 relatives of affected individuals was 3-4 per cent. [figures corrected by abstracter] that among male relatives being 1-9 per cent., and among females 4-6 per cent.; of the 775 relatives who were over 50 years of age, 5 per cent. were affected. Of 2,759 relatives of patients in the control group, 0-58 per cent. were affected (males 0-52 per cent., females 0-64 per cent.), the incidence among the 1,530 who were over 50 being 1-1 per cent. Lack of agreement between the observed numbers of sibships having 0, 1, 2, 3, and 4 cases of the disease, and those expected on the basis of the Poisson distribution provides further evidence of a familial tendency. While the ratio of females to males among all affected relatives was approximately 2:5 to 1, any question of transmission of susceptibility to the disease as a sex-linked factor was ruled out by examination of pedigrees. There was found to be no association between parity and susceptibility.

After correcting for small family size and for age, the data are consistent with transmission as an autosomal dominant gene with approximately 50 per cent. penetrance or as an autosomal recessive gene with about 70 per cent. penetrance, but the latter hypothesis was ruled out in the extensive pedigree (including ten cousin marriages) reported by Whittinghill and Hendricks (J. Elisha Mitchell Sci. Soc., 1951, 67, 185). From estimates of the incidence of rheumatoid arthritis in the population of the whole area concerned, the gene frequency as a dominant with 50 per cent. penetrance would be 0-006, and as a recessive with 70 per cent. penetrance, 0-091.

The authors discuss the variations in penetrance and excessive irregularities of expressivity of the hereditary factor in rheumatoid arthritis in relation to the various internal and external ancillary aetiological factors involved.

R. H. Cawley.


The author prefixes this paper with a detailed description of the anatomy and function of the normal hand and of special reference being made to the metacarpophalangeal joint. The sequence in the development of deformities as a result of rheumatoid arthritis is then described, the main deformities being subluxation and flexion of the metacarpophalangeal joint due to a loose capsule, and ulnar deviation due to gravity and unequal muscle forces.

A programme of exercises to be given by the physiotherapist is outlined, the aim of the exercises being correction of the alignment of the phalanx on the metacarpal, followed by extension of the metacarpophalangeal joint, and finally by extension of the phalangeal joints. In closing the hand, flexion of the phalangeal joints should be carried out first and then flexion of the metacarpophalangeal joint.

J. B. Millard.


Artsiony Therapy in Rheumatoid Arthritis. LEFKOVITS, A. M. (1953). Rheumatism, 9, 70. 5 figs, 15 refs.


Ocular Manifestations of Still's Disease. (Les manifestations oculaires de la maladie de Still.) BONNET, P., and BONNET, I. (1953). Bull. Soc. Ophthal. Franc., 379. Band-shaped keratitis, plastic iritis and cataract are the most common ocular manifestations of this affection which is similar to chronic polyarthritis. J. Rouget.

(Osteo-Arthritis)


This is a detailed statistical analysis of 264 cases of congenital dislocation of the hip treated at the Royal National Orthopaedic Hospital, London, in the period 1891-1940. The cases analysed are those in which the patient was traced and examined during the years 1949-50, and are regarded as presenting a more favourable picture than would probably be found in the whole series of 889 cases treated during the 50-year period. [The report does not easily lend itself to condensation and the reader is recommended to study the original. Some of the conclusions drawn by the authors are summarized below.] The results of closed reduction gave "reason for sober satisfaction", being satisfactory in four-fifths of the unilateral cases and in two-thirds of the bilateral cases if treatment was instituted before the age of 3 years. Immediate open reduction gave only moderate results in the nine cases studied. Of secondary operative procedures, the shelf operation was the most successful, giving encouraging results in two-thirds of the cases. In general, the outcome of open reduction was bad, the results being satisfactory in only four out of twenty cases. Rotation osteotomy "presented a dismal picture", having been effective in only four out of nine cases. The effective life of the successfully treated hip appears to be between 25 and 30 years, after which the joint becomes troublesome in about 50 per cent. of cases. John Charnley.


The authors record and discuss cases of hip-joint deformity observed during routine examinations at the Cerebral Palsy Clinic of the Children's Hospital, Los Angeles, between 1947 and 1952. Among 1,243 patients, ranging in age from infancy up to 19 years, 162 with clinical signs suggestive of hip-joint derangement were noted, and radiographic evidence of abnormality was found in 32 (2.6 per cent.). The deformity was congenital in type in six and non-congenital in 26 (eight with dislocation and eighteen with subluxation or migration of the femoral head). Cases of the latter type were characterized by a valgus position of the femoral head and neck with relation to the shaft, the angle being 150 degrees or more in 23 cases, tear-drop deformity of the head in fifteen cases, and normal acetabulum in all. The majority of the patients suffered from severe spastic quadriplegia, and fifteen of them had never stood or walked to any appreciable extent. Sex distribution was equal, and half were under 5 years of age. Typically, the flexor, adductor, and internal rotator muscles of the hip were stronger, tighter, and more spastic or rigid than those of the opposing groups.

In the majority of cases operative treatment would have had little hope of success either on account of the severity of the condition or the low intelligence of the patient. In six cases of the non-congenital group with migration of the femoral head, however, tenotomy of the adductor longus muscle and neurectomy of the anterior branch of the obturator nerve were performed, followed by straight traction in wide abduction, and resulted after 4 months in a satisfactory position of the femoral head, improvement in walking or standing, and facilitation of nursing care. The authors recommend periodic x-ray examination of the pelvis in all cases of cerebral palsy, and are of the opinion that whenever a
valgus of the femoral neck of more than 150 degrees is present, early dislocation of the hip joint may be expected.

V. Reade.


In an investigation at the Nuffield Orthopaedic Centre, Oxford, of the blood supply to the femoral head in 36 adult specimens obtained post mortem, injections of barium sulphate suspension, silver iodide solution, Berlin blue, and “neoprene latex” solution were made into the medial circumflex femoral artery, the common femoral artery, or the common iliac artery. The barium-sulphate and silver-iodide methods permitted radiological examination of the specimen, either complete, or after sections had been made. Latex casts of the vascular tree, obtained by digestion of the bone and marrow with acid, were dissected under water.

It was found that the vascular patterns established during growth and delineated by the cartilaginous epiphyseal plate persist throughout adult life, and the vessels entering the head may thus be termed metaphyseal or epiphyseal, after the origin of the area which they supply. From the medial circumflex femoral artery arise superior and inferior metaphyseal and lateral epiphyseal vessels, and from the acetabular branch of the obturator artery a branch passes along the ligamentum teres to form the medial epiphyseal artery. The lateral epiphyseal vessels, two to six in number, enter the femoral head posteriorly in a thick fibrous sheath, passing transversely above the epiphyseal scar to supply most of the head of the bone. The medial epiphyseal artery enters the pit on the head of the femur, supplies a small area of surrounding bone, and anastomoses with the lateral epiphyseal system. The final distribution of the epiphyseal vessels is through a series of radially-arranged vessels which unite to form arcades as they pass towards the articular cartilage. On the upper aspect of the femoral neck, two, three, or four superior metaphyseal arteries enter the bone. These pass at first vertically downwards, and then return medially towards the epiphyseal scar. The inferior metaphyseal arteries enter the undersurface of the neck close to the articular cartilage. The metaphyseal and epiphyseal circulations anastomose across the epiphyseal scar, the anastomotic vessels often showing a spiral formation.

These investigations do not demonstrate any diminution in the blood supply to the femoral head with advancing age. The situation of the main epiphyseal arteries laterally may explain why these vessels are more liable to injury in adduction than in abduction fractures of the femoral neck and the higher incidence in the former of avascular necrosis of the head of the femur.

Peter Ring.


The authors have treated eighty cases of chronic joint disease, of which 68 were cases of osteo-arthritis (mainly of the knees) with phenylbutazone (“Butazolidin”). The drug was injected intramuscularly in doses of 1 g. in a 20 per cent. solution to which a local anaesthetic had been added, and there were few local or general reactions. The effect was apparent in some cases within 30 minutes, though usually 12 to 24 hours were required. In twelve cases the effect lasted 1 to 3 days, in 48 cases 1 to 2 weeks, and in sixteen cases 4 weeks or longer. The average number of injections was two or three.

Improvement, both objective and subjective, was noted in the greatest benefit being obtained in arthritis of the knees and the least when the spine was affected. Of the eighty patients treated, 24 derived prolonged benefit, and 52 substantial relief; four were unaffected.

(In an addendum it is stated that the number of cases treated has subsequently risen to 220, the results obtained being similar to those in the smaller group.)

D. Preiskel.


(Spondylitis)


This article describes the treatment with cortisone of eleven cases of spondylitis, disabled, but considered to be capable of improvement to full wage-earning capacity. These 11 cases, who had previously been under observation and treatment by other methods, without restoration of wage-earning capacity, were treated with an initial course of cortisone, designed to bring about maximal symptomatic remission, and then stopped, with further “booster” courses of 5 to 10 days' duration, were given as thought necessary, the main indication being increasing functional impairment. The dose was usually 100 mg. per day, either orally or by intramuscular injection.

On the criterion of work capacity, four of these patients showed marked improvement and four others moderate improvement. After 24-30 months on this regime, ten of the eleven patients were in employment on a full-time basis.

The only side-effects encountered were reactivation of controlled epilepsy, during the initial course, in one patient, and gastro-intestinal haemorrhage in two others (which the authors do not ascribe to the cortisone therapy). They consider that this form of treatment has
produced good results, and that it has advantages over the continuous administration of cortisone.

B. E. W. Mace.


The author reports on fifteen patients, eleven men and four women, ranging in age from 44 to 78, who complained of pain in the cervical-dorsal spine of varied duration. Radiography showed typical calcification of the anterior longitudinal spinal ligament, giving an appearance which has been likened to that of sugar-icing. These changes were best seen in the cervical and mid-dorsal spine; they are not to be confused with those occurring in spondyritis ankylopoietica or chronic fluorine poisoning.

In contrast to Forestier and Rotés-Querol, who in 1950 described a similar condition under the name of "hyperostose ankylosante sénile" and believed it to be confined to males, the author is able to include four females in his series. He rightly points out that this spondylosis of middle and old age is the condition first described by von Bechterew, while the priority for describing ankylosing spondylitis belongs to Strümpell and Marie. A further point of difference between the two conditions lies in the pathogenesis. Ankylosing spondylitis is to be reckoned among the inflammatory diseases, this word being used in its widest sense, while the disease described in this paper belongs to the degenerative arthroses.

L. Michaelis.

**(Miscellaneous)**


In this paper from the University of Liverpool the natural history of lupus erythematosus is discussed and the close relationship between the chronic discoid and acute systemic forms of the disease is demonstrated by reference to sixteen cases.

The typical chronic discoid rash was observed in nine cases of lupus erythematosus. On pathological examination no evidence of an increase in the erythrocyte sedimentation rate (E.S.R.) was found and tests for the presence of "L.E." cells were negative. Minor abnormalities included leucopenia and an increase in the serum globulin level. In a further group of seven cases major systemic reactions were observed. One patient, a woman aged 47 years, suffered from chronic discoid lupus erythematosus for 2 years before systemic changes, such as arthritis, pleural effusion, and loss of weight, were noted. After these symptoms had subsided "L.E." cells were still present in the blood. In the remaining six cases in this group the systemic manifestations were increasingly severe. The authors believe that the evidence presented by these cases favours a unitary conception of the disease—for example, the typical chronic discoid rash developed in a woman, aged 40 years, with rheumatoid arthritis, hepatitisplenomegaly, pyrexia, leucopenia, and a raised E.S.R. The response to administration of cortisone or ACTH was minimum in patients suffering from the chronic discoid form of the disease; on the other hand, there was a dramatic improvement in response to these drugs in four patients with systemic lupus erythematosus. Cortisone was given by mouth in a dose of 25 mg. four times daily and ACTH by intramuscular injection in a dose of 25 mg. every 6 hours. All except one of the patients were finally maintained on a daily dose of cortisone which ranged from 37.5 to 75 mg. daily, the exception being a patient who received a maintenance dose of 10 international units ACTH gel at intervals of one week. Although permanent remission was not obtained, the authors believe that the hormone therapy was justified in the cases of acute systemic disease. This treatment should not, however, be given to patients with a mild form of the disease, for spontaneous remissions are obtained less readily in such cases; moreover, hormone therapy may precipitate a systemic spread in patients with chronic discoid lesions.

A. Garland.


The introduction of cortisone and corticotrophin in the treatment of lupus erythematosus has emphasized the lack of real knowledge of the natural history of this disease. The authors have reviewed 44 cases of the disorder seen at the Columbia-Presbyterian Medical Center, New York, in the past 15 years, together with 279 reports published in the literature during the period 1948-52. The diagnosis of lupus erythematosus disseminatus in the authors' own cases was based on the ten criteria laid down by Brenner and others (Amer. J. med., 1948, 5, 288); only those cases were selected from the literature in which at least seven of these diagnostic criteria were fulfilled.

Information as to presenting symptoms was available only in the authors' cases, arthralgia being observed in 48 per cent., fever in 25 per cent., malaise in 18 per cent., loss of weight in 14 per cent., skin lesions in 14 per cent., and Raynaud's phenomenon in 11 per cent. Fever was present at some time during the illness in nearly all the cases reviewed. Rashes were observed in 69 per cent. of the authors' cases and in 84 per cent. of those culled from the literature; arthritis or arthralgia in 76 and 77 per cent. respectively; and cardiac manifestations in 70 and 68 per cent. respectively. Comparative information relating to other symptoms and signs and to laboratory and necropsy findings is given. Of the authors' patients 13 (30 per cent.) were alive after 5 years. In the reports from the literature it was much more difficult to determine the time of onset of symptoms, but in 22 per cent. of cases in which assessment was possible, the patient was alive after 5 years.

R. E. Tunbridge.


The authors define the pararheumatic arthropathies as the musculo-articular manifestations occurring in the
Some Effects of Nitrogen Mustard and Triethylene Melamine in Acute Disseminated Lupus Erythematosus.


As difficulty is often encountered with the use of corticosteroids in the treatment of disseminated lupus erythematosus, five patients at the Indiana University Medical Center, Indianapolis, were treated with nitrogen mustard, and two of them with triethylene melamine as well. The duration of remission of signs and symptoms after administration of these drugs varied from 6 days to a maximum of 217 days, as compared with 14 to 300 days after treatment with ACTH. Since in most of the patients there was impaired bone-marrow function as the result of the disease the total dosage of nitrogen mustard was limited to 0.4 mg./kg. body weight. The authors do not consider that nitrogen mustard and triethylene melamine are effective solely through adrenal cortical stimulation; their mode of action, therefore, must remain speculative.

It is suggested that treatment with nitrogen mustard in combination with corticosteroids might be beneficial in these cases.

Geoffrey McComas.


The report authors, from the Hospital of the Rheumatism Foundation, Heinola, Finland, the results of skin tests with "Trafuril" (an ointment containing 5 per cent. tetrahydrofurfuryl nicotinic acid ester) in 269 cases of rheumatism (mainly rheumatoid arthritis) and 69 healthy control subjects. The application of trafuril to the skin resulted in an erythematous reaction within 10 or 15 minutes in all the controls, in the two cases of pururatum rheumatica, and in all eight cases of osteo-arthritis. In about two-thirds of the remaining cases (consisting of 228 cases of rheumatoid arthritis, sixteen of ankylosing spondylitis, and two of psoriatic arthritis), the result was negative, a positive reaction occurring mainly in early cases and in children with rheumatoid arthritis. After treatment with ACTH (corticophrin) or cortisone, or after the development of complications of gold therapy, a positive reaction frequently developed in cases in which it had previously been absent. Kathleen M. Lawther.


In this paper fifteen cases of progressive systemic sclerosis (scleroderma) are described in detail from the Peter Bent Brigham and Robert Breck Brigham Hospital, Boston. The average age of onset was 40 (range 19 to 52) and all the patients but three were women. All fifteen patients had constitutional symptoms, and showed the characteristic thickening of the skin of the hands. The authors were impressed by the frequent involvement of other systems; for example, twelve had joint pain or swelling, fourteen had cardio-respiratory embarrassment, and eleven had gastro-intestinal symptoms. The majority had no abnormal signs in the heart and lungs, seven patients showing abnormal chest radiographs in which there was linear streaking at the bases and alteration of the cardiac outline. Electrocardiographic changes were common; these were largely non-specific, and included inverted T-waves, low voltage complexes, and arrhythmias.

Post-mortem examination of five of the six fatal cases confirmed the widespread visceral changes typified by microscopical fibrosis in the myocardium, lungs, gastro-intestinal tract, kidneys, and liver. Corticotrophin and cortisone therapy was tried in nine cases, but only one patient seemed to benefit. Other treatment with melanocyte hormone preparations, vitamins, and peripheral vasodilators gave consistently negative results.

The authors suggest that in view of the widespread distribution of the lesions in scleroderma and of histological findings, this disease must be regarded as an antigen-antibody allergic reaction of the mesenchymal tissues, resembling acute disseminated lupus erythematosus in this respect, but differing from it in its slow response to the allergic reaction and in the predominance of fibrosis and sclerosis. One of the authors' patients presented simultaneously some of the features of both diseases, indicating in their opinion a relationship between the two.

K. C. Robinson.

Treatment of Rheumatoid Arthritis with Phenybutazone.


The authors have investigated at the London Hospital the effect of phenylbutazone ("Butazolidin") in a series of 57 patients suffering from rheumatoid arthritis. Alternate patients were given either phenylbutazone or an inert substance, the dose of phenylbutazone being 200 mg. three times a day for 4 weeks, and neither the patients nor the doctors assessing progress knew which substance each patient was given. Patients were examined before the trial and again after 28 days; subjective improvement was assessed by the relief of pain and joint stiffness and improved ability to perform routine tasks, objective improvement by alterations in the diameter and range of movement of the joints.

The results for 55 patients who completed the course were analysed statistically. The number of patients...
showing subjective and objective improvement was significantly greater in the group given phenylbutazone than in the control group, 22 patients receiving phenylbutazone showing subjective improvement as against eleven in the control group, while the figures for objective improvement were twelve and five respectively. No significant change in the haemoglobin values, leucocyte count, or erythrocyte sedimentation rate was noted in those treated with phenylbutazone, and these patients also showed an average gain in weight after 2 and 4 weeks of treatment which was statistically significant. In three patients toxic effects were so severe that treatment with phenylbutazone had to be discontinued.

The effect of the drug on another, larger, but uncontrolled, group of 164 patients is also presented, particular attention being paid to toxic effects. These patients received the drug for periods varying from 1 to 6 months. Toxic effects occurred in 40 per cent. of the cases, and were severe enough in half of these for treatment to be stopped, but in the other half the toxic effects wore off although treatment was continued. The chief complications were indigestion and nausea (28) and skin eruptions (15). Other complications occurring fairly frequently were diarrhoea, sore mouth, oedema, and lymphadenopathy. No case of agranulocytosis occurred. The authors are of the opinion that because of the potential danger of phenylbutazone the drug should be given only under strict medical supervision.

C. E. Quin.


These two papers both deal with the secondary toxic manifestations of phenylbutazone ("Butazolidin"). In the first, the authors report the occurrence of toxic symptoms in 46 (42 per cent.) of 109 patients with rheumatoid arthritis, osteo-arthritis, or gout, given an average daily dose of 0-6 g. by mouth with restricted salt intake. [This figure is to be compared with the over-all figure of 22 per cent. for cases published in the literature which is cited in the second paper.] Considerable symptomatic improvement was noted in 59 cases, but was unassociated with any reduction in the erythrocyte sedimentation rate. The toxic effects were generally similar to those previously reported and were found to occur usually after 3 weeks of treatment.

The author of the second paper briefly reviews the literature and reports in detail two cases of blood dyscrasia attributable to the drug, one being a case of fulminating aplastic anaemia and the other a case of agranulocytosis with uneventful recovery. There was no evidence that the toxic reactions bore any relation to dosage. In the fatal case, which was diagnosed as one of rheumatoid arthritis, the patient had previously suffered from myxoedema, which had responded to treatment with thyroid, and had also been treated with ACTH (total dose 0-82 g.) and with gold (total dose 0-44 g.). The possibility is discussed that the anaemia might have been due to the previous gold therapy or that the patient had thereby become sensitized to phenylbutazone.

Harry Coke.


Fatal Agranulocytosis and Gastric Ulceration due to Phenylbutazone. DILLING, N. V. (1953). Lancet, 1, 1230. 19 refs.


Recent Investigations on Phenylbutazone. An Experimental Study. (Ulteriori indagini sul fenilbutazone. Studio sperimentale riguardante la sua eliminazione nelle urine e nei liquidi organici ed il comportamento del "test dell'uropepsina"). LUCHERINI, T., NATALE, P., CONESTABLE, E., and CERIMELE, E. (1953). Reumatismo, 5, 303. 5 figs, 5 refs.


Treatment of Chronic Joint Disease with "GT 50" (Vitamin D.). (Le traitement des arthroses par le GT 50.) GAUTIER, A. (1953). Praxis, 42, 709. 3 refs.


Disk Syndrome
Lumbar Disk Lesion Syndrome. ARMSTRONG, J. R. (1953). Rheumatism, 9, 82.


Gout

The author reviews the literature relating to the importance of urate deposition in chronic gout and of the reduction of the serum uric acid level in its treatment, and discusses the two available approaches to the therapeutic problem—by restriction of diet, and by the reduction of tubular reabsorption of urates in the kidneys by means of certain drugs, with particular reference to sodium salicylate.

He then describes the results of investigations carried out at the General Hospital, Birmingham, on 32 patients with chronic gout which had persisted for at least 3 months and was unrelated by colchicine therapy. The effect of diet on the serum uric acid level was studied in eight male patients who received alternately low- and high-purine diets, each for a period of 7 to 11 days. In seven of the eight patients the change from a low- to a high-purine diet was accompanied by a rise in the serum uric acid level, but the change was slight in degree and insufficient, in the author’s opinion, for a low-purine diet of therapeutic value.

Continuous sodium salicylate therapy in a daily dosage of 60 to 140 gr. (4 to 9 g.) was then attempted in 29 cases and was maintained in fourteen of them for more than a year. In only one case did it prove impossible to reduce the serum uric acid level to within normal limits, and this patient was the only one with severe renal impairment. Intermittent treatment (for three consecutive days, in each week) failed to maintain the reduction. All the patients experienced marked subjective improvement while receiving salicylates. In a few cases improvement was delayed for several weeks, but once started it was progressive. Reduction in the size of tophi took place and in two instances tophi disappeared completely. Marked radiological improvement was observed in four cases. The maintenance of the serum uric acid content at a normal level did not necessarily prevent the occurrence of acute gouty attacks, for which colchicine was prescribed and usually afforded relief. Symptoms of salicylism usually appeared on starting treatment, but in most cases good tolerance developed after the first month. No haemorrhagic manifestations were observed. Vitamin K being given when the plasma prothrombin concentration, which was estimated at frequent intervals, fell below 25 per cent. of normal.

The author claims to have shown very conclusively that continuous administration of sodium salicylate, in the absence of nephritis, can lower the serum uric acid level in chronic gout and thus ameliorate the symptoms and reduce the disability. R. E. Tunbridge.


This type of iritis is always unilateral and is of marked onset. The signs are deep and acute and the anterior chamber is filled with exudates and blood. Treatment with colchicine gives complete and rapid recovery. J. Rougier.


In a known case of gout, fine needle-like crystals were seen in the bulbar conjunctiva in the inter-palpebral space. The deposits, which were asymptomatic, were proved to be urate salts by biopsy and the murexide test. Redmond Smith.


General Pathology


The authors give details of a new spectrophotometric method developed at the Children’s Medical Center (Harvard Medical School), Boston, for the determination of a 50 per cent.-haemolytic end-point in the estimation of serum complement. Using this technique, which they consider to be far more sensitive than the normal routine methods at present in use, they studied the quantitative changes in serum complement level in seventy children suffering from various collagen diseases. The initial figures were below normal in lupus erythematosus (4), acute glomerular nephritis (20), and nephrosis (15), and greater than normal in anaphylactoid purpura (14), dermatomyositis (6), and rheumatoid arthritis (11). In the three disorders in which the serum complement value was initially low, a rise occurred in association with clinical improvement, however induced. There was no evidence of anti-complementary activity in the serum. The low serum complement level before treatment cannot be explained as the result of protein loss during the acute phase, as there is no correlation between the degree of urinary protein excretion and the serum complement level, and would appear to support the theory that these diseases are allergic in nature, serum complement being depleted by certain gross antibody-antigen reactions.

The significance of the high serum complement values in rheumatoid arthritis, dermatomyositis and rheumatic fever is discussed, and it is suggested that such findings do not exclude the possibility of an immunological mechanism in the pathogenesis of these diseases; the differences in serum complement titre may reflect differences in the relative quantities, types, or location of the antigens and antibodies involved, or in the time relation between stimulus and reaction. R. E. TUNBRIDGE.


On the basis of observations made at the Institute of Histopathology, University of Zürich, the author considers that the primary lesion in the Aschoff body in rheumatic myocarditis is tissue necrosis, and that this necrosis may occur not only in connective tissue, but also in muscle fibres. The cellular reaction which develops for the reabsorption of these necroses consists mainly of basophil histiocytes, which may be converted into Anitschkow cells. These Anitschkow cells are not myocytes—for besides being seen in the myocardium they also occur in the endocardium and epicardium—but are the form taken by basophil histiocytes in the heart (to which Anitschkow cells appear to be limited) in rheumatism and endocarditis lenta, and in the healing of experimental wounds of the heart and of cardiac infarcts.

The structure of the granuloma, however, provides no evidence regarding its cause, but it is suggested that streptococcal infections and associated allergic factors may be responsible. C. L. OAKLEY.


Subcutaneous nodules were excised from the elbow region in twelve cases of rheumatic fever at the Canadian Red Cross Memorial Hospital, Taplow, freed by micro-dissection from adjacent tissue, washed, dried, and extracted with benzene and light petroleum to remove fatty material. Specimens of normal connective tissue obtained post mortem were treated similarly. (The authors give full details of all methods.) After auto-claving with water at 120° C. for 3 hours to remove collagen, the rheumatic nodules yielded a residue varying between 25 and 40 per cent. of the original weight, whereas the residue from non-rheumatic connective tissue gave only 10 per cent. residue. The extracts of the two tissues thus obtained, after hydrolysis with hydrochloric acid, gave similar chromatograms which resembled those obtained by Bowes and Kenten (1949) for collagen. The chromatograms of the residues, however, differed markedly, those from non-rheumatic connective tissue yielding findings suggestive of elastin, while those from the rheumatic-nodule residues suggested the presence of tyrosine-rich protein or polypeptide in addition to elastin; this substance appeared to be present also in non-rheumatic tissue, but in much smaller amount. Analysis of the sugars released on hydrolysis suggested that the polysaccharide components normally present in subcutaneous connective tissue are also present in rheumatic nodules, but in greater quantities. The higher content of non-collagen protein and of polysaccharide in the nodules may be due either to increased deposition of these substances or to the destruction and removal of collagen. The presence of a tyrosine-rich protein and of polysaccharide in both rheumatic and non-rheumatic tissue indicates the presence of substances other than collagen and elastin, possibly forming part of the inter-fibrillar ground substance, which is generally considered to be mucoprotein in nature. There was no evidence of the presence of large quantities of fibrin in the nodules.

R. E. TUNBRIDGE.

This paper from the Centre for the Investigation of Rheumatic Diseases, Nether Edge Hospital, Sheffield, describes a method for estimating urinary steroids derived from the adrenal cortex. Certain corticosteroids (17 : 20 : 21-triols and 17 : 20-glycols) on oxidation with periodic acid yield 17-ketosteroids which can be easily estimated; this procedure is in general use. Norymberski has shown that by substituting sodium bismuthate for periodate as the oxidizing agent it is possible to extend the estimation of these 17-ketogenic steroids to include corticosteroids with a dihydroxyacetone side-chain (17 : 21-diol-20-one). In the present paper the term "17-ketogenic steroids" is used to denote these converted by bismuthate (not by periodate) into 17-ketosteroids. Urine 24-hour samples, collected without preservative and diluted with distilled water up to 2 l., were assayed in duplicate for 17-ketosteroids and for "total 17-ketosteroids" (after bismuthate oxidation), the difference between the two levels representing the 17-ketosteroids derived from 17-ketogenic steroids on oxidation. The experimental procedure was adapted from that of Dreket and others (J. clin. Endocr., 1952, 12, 55), and has been fully described in a previous paper (Norymberski, Nature (Lond.), 1952, 170, 1074).

By this method the recovery of added corticosteroid is 80 per cent. or more.

The output of 17-ketogenic steroids of normal men and women, and of children, was determined and compared with that of patients with various diseases. In cases of rheumatoid arthritis and ankylosing spondylitis the output was about 40 per cent. lower than in normal adults; treatment with ACTH caused increased output, which varied irregularly with dose and subject. In patients treated with cortisone acetate there was a linear relation between the size of dose and the excretion of 17-ketogenic steroids, indicating that the assay of the latter gives a measure of adrenal activity, 17x-hydroxycorticosterone, the main cortical steroid, being probably excreted as a dihydroxyacetone derivative.

This simple method has the great advantage that it does not require hydrolysis by strong acid, thereby avoiding destruction of corticosteroids. Nancy Gough.


After a review of previous work on the significance of the presence in the serum of antibodies to group specific streptococcal polysaccharides in the rheumatic diseases, the author details his own findings at the Massachusetts Memorial Hospitals (Boston University School of Medicine) in sera from 151 patients with streptococcal infections, 76 patients with acute rheumatic fever, and 310 patients with other diseases. The precipitating antibody for purified group-A carbohydrate was detected by layering the bacterial extract over the serum and incubating at 37° C. for 2 hours and then transferring to a refrigerator. Readings were made at 24, 48, and 72 hours, control tubes being set up containing bacterial extract and saline or serum and saline. (The details of preparation of the bacterial extract containing group specific polysaccharide are given in full.) Serum was obtained from each patient at the time of admission and again 14 days later. A positive precipitin reaction was obtained in 34 per cent. of the group with streptococcal infections (without non-suppurative complications), in 24 per cent. of the group with acute rheumatic fever, and in proportions ranging from 0 to 100 per cent. in the various other diseases. These results are somewhat at variance with other published results, possibly owing to the author's method of purification of the extract, which is simpler than that usually employed but is claimed to be more efficient. The extract was free from type specific nucleoprotein, since there was no precipitation with type-3 specific antiserum.

The author concludes that antibody may frequently be present in a patient's serum without other evidence of streptococcal infection, that its absence does not exclude the presence of streptococcal infection or rheumatic fever, and that hypersensitization to group-A specific polysaccharide is of no significance in the pathogenesis of the rheumatic state.

E. G. L. Bywaters.


Comparisons of the mean titre of antistreptolysin-O (AST) in the serum of non-rheumatic children and of children with active rheumatic fever have not hitherto revealed differences sufficiently great to provide a reliable diagnostic test, although a low or absent AST may provide confirmatory evidence of the absence of active rheumatic fever. The present author, working at the University of California, attempted to discover whether a minimum titre could be established to provide a "diagnostic exclusion index". Serum was therefore obtained from individuals under 21 years of age who were classified after examination (at a number of centres) as follows: 2,147 normal children; 2,988 with illness other than active rheumatic fever; 197 with active rheumatic fever. AST determinations were made by the technique of Rantz and Randall (1945), using stable, reduced, desiccated streptolysin-O, a number of different laboratories participating in the work. The reproducibility of results as between laboratories was tested and found satisfactory.

In all three groups there was a significant degree of variation in titre between sera from different parts of the United States. Nevertheless, analysis of the combined results for non-rheumatic subjects showed that in all but one of the geographical areas at least 30 per cent. of sera gave AST values of less than 100 units per ml., whereas less than 5 per cent. of sera from cases of active rheumatic fever gave AST values in this range. The author notes that the AST values in 1,142 cases of rheumatic fever reported in the literature, all but two were above the level of 50 units per ml. He therefore suggests that a titre of 50 units or less per ml. obtained repeatedly in the
same case is a highly reliable "exclusion index" for rheumatic fever.

[It is not clear from the text whether in selecting the cases of active rheumatic fever the duration of the disease was taken into consideration. If cases with activity of long duration were included, these results must be taken to support Coburn's original view that a rise in serum antistreptolysin titre is directly related to the activity of the disease.]

E. J. Holborow.


The structure of the early subcutaneous nodule of rheumatoid arthritis was studied at the New York University and the Bellevue Hospital. It is postulated that one of the primary morphological changes in rheumatoid arthritis is an arteritis and that the developing nodule, evoked probably by trauma, is seen microscopically as an active localized proliferation of the involved blood vessels with, spreading out from them, a granulation tissue in which there appears necrosis of the fibres and a reactive cellular response (palisades). The process is thought to be centrifugal, possibly due to a toxic effect from the vessels, the nodule differing from that of acute rheumatic disease only in the greater degree of necrosis.

A. C. Lendrum.


ACTH, Cortisone, and Other Steroids


In an attempt to demonstrate the action of hydrocortisone and cortisone on the skin lesions of sarcoïdosis five patients at the Hospital of the University of Pennsylvania with histologically proven sarcoïdosis of 2 to 11 years' duration received local injections of these substances in close proximity to cutaneous sarcoïd lesions. Injection of 2.5 mg. hydrocortisone into eighteen lesions resulted in initial regression in 3 to 7 days and complete or nearly complete resolution in 14 days. In three patients ten lesions recurred within 4 to 7 weeks of the injection, but they were one-third smaller than before treatment. In two patients in whom five lesions were treated there was no evidence of recurrence 4 to 14 weeks later, at which time administration of cortisone by mouth was begun.

Examination of biopsy specimens of the treated lesions 7 days after the infiltration revealed typical sarcoïd granulomata; examination 14 days after the treatment showed no residuum of the sarcoïd lesions. The most striking histological finding was the presence in the corium of basophilic granular material, subsequently shown to be hydrocortisone acetate, around which there was no cellular reaction.

Injection of cortisone resulted in a similar but less striking regression of the lesions. There was no change in skin lesions not subjected to local infiltration of hydrocortisone or cortisone, and less concentrated preparations resulted.

After this part of the investigation was completed, four patients were given 25 mg. cortisone by mouth four times daily for 6 weeks. In 1 to 2 weeks the skin lesions began to diminish in size until at 4 to 6 weeks resolution was about two-thirds complete. Two weeks after cessation of treatment all the skin lesions began to relapse, and in three of the four patients numerous new lesions appeared; this was considered to be a "rebound" phenomenon.

It is concluded that in selected cases local administration of hydrocortisone may influence the course of cutaneous sarcoïdosis.

D. W. Barritt.


The authors report their results in a preliminary trial at the Hôpital Lariboisière, Paris, of hydrocortisone injected intra-articularly in 24 patients with rheumatoid arthritis, of whom nineteen were already undergoing treatment with cortisone. Their observations suggest that the maintenance dose of cortisone may be considerably reduced if one or more joints in which active disease is persisting are treated locally with hydrocortisone. In fifteen patients given intra-articular injections of hydrocortisone the pain, swelling, and stiffness diminished and sometimes disappeared, and in all of them it was possible to reduce the maintenance dose of cortisone without...
relapse. In one patient with ankylosing spondylitis accompanied by arthritis of a hip-joint, local treatment of the hip brought rapid relief, and it was found possible to reduce the maintenance dose of cortisone from 125 to 75 mg.

Kenneth Stone.


The effect of the intra-articular injection of cortisone is uncertain and transitory. Although hydrocortisone (Kendall's Compound F) has the same therapeutic properties as cortisone it is unexpectedly efficacious when applied locally. The authors report their results in 130 patients at the Instituto Reumatología, Lisbon, suffering from a wide variety of rheumatic diseases, principally rheumatoid arthritis and osteo-arthritis, and treated with hydrocortisone. The most effective dose for injection of large joints was found to be 25 mg., and for smaller joints 8 to 15 mg.

In cases of rheumatoid arthritis the inflammatory signs disappeared first; in some cases relief of pain, easier though restricted movement, and reduction in swelling lasted up to 3 weeks, but lessened after 7 to 10 days. In osteo-arthritis the relief was more lasting. The return of symptoms is the deciding factor as to whether, and when, injections are to be repeated. In general, they were given weekly in rheumatoid arthritis. The authors stress that the secret of success is that the injections shall be truly intra-articular, particularly in affections of the hip-joint; the technique is described in some detail. No generalized effects were noted, the action of the hormone appearing to be purely local: for instance, in no case was improvement in a polyarthritis observed, except in the joint treated.

The effect of hydrocortisone is not specific, as disorders of the most varied aetiology, such as traumatic conditions, osteo-arthritis, rheumatoid arthritis, rheumatic fever, tenosynovitis, and sciatica respond equally well. In the 37 cases of rheumatoid arthritis, all signs of activity of the disease disappeared in six patients after six to eight injections; 29 patients were improved, and only two were unaffected. Improvement followed in all of 28 cases of osteo-arthritis of the knee, and was good but less satisfactory in seventeen cases of osteo-arthritis of the hip. The authors point out that this therapy is not curative; relief of pain in an osteo-arthritic knee, even for several months, does not imply cure, for the same morbid process continues; and in rheumatoid arthritis symptoms recur sooner or later when the injections of hydrocortisone are stopped.

Kenneth Stone.


In this series of 87 patients with rheumatic diseases treated at the Hôpital Lariboisière, Paris, by intra-articular injections of hydrocortisone, the dose at each injection was 25 mg. and injections were given once weekly at first.

In 25 patients with osteo-arthritis of the knee the results were very good or good in seventeen (68 per cent.). In five of these, one, two, or three injections brought amelioration lasting 1 to 2 months. In the eight cases showing a less satisfactory response, pain returned after each injection in from 1 to 3 weeks. In a group of 25 patients with osteo-arthritis of the hip, the results were less striking, but fourteen cases (56 per cent.) were relieved. One patient obtained lasting relief after five injections; in others, relief after each injection lasted only 3 or 4 weeks. Hydrocortisone was also given to 21 patients with scapulo-humeral peri-arthritis. In cases with acute or subacute sub-acromial bursitis in which pain was the predominant feature, the effect was in every case excellent. It was less good in conditions of long duration in which there was much restriction of movement owing to adhesions.

Kenneth Stone.


After quoting the results claimed by other workers in the treatment of chronic articular rheumatism with intra-articular hydrocortisone, the author reports his own experience at the Institute for Physical Therapy of the University of Zürich in eighteen cases of rheumatoid arthritis. The dose of hydrocortisone given at each injection was 5 mg. for finger and toe joints, 10 mg. for the head and neck, 20 mg. for the elbow, 20 to 30 mg. for the shoulder, and 40 to 50 mg. for the knee. However, no attempt was made at local treatment until the general health of the patient had been improved as far as possible by other means, such as blood transfusion, gold injections, and administration of cortisone, and only those joints which did not yield to these general measures were injected with hydrocortisone.

A detailed analysis of the results is difficult in view of the polytherapy used, but several individual cases are described. In general, relief of pain and swelling resulted from the injection, enabling effective physiotherapy to be carried out. Injections had to be repeated at intervals of 10 to 14 days, though the interval could usually be gradually extended. Some patients were fortunate in that the local inflammatory reaction cleared up after only one or two injections, but in one case quoted, 105 injections into eight joints were required.

In the opinion of the author, the intra-articular injection of hydrocortisone by itself is not enough, its effect being entirely local.

D. Preiskel.


Historical considerations show that sodium salicylate has always in the past been held to act in accordance with the currently accepted theory of the aetiology of
rheumatism. Thus it is not surprising that the discovery of the effect of cortisone in rheumatoid arthritis was soon followed by reports of the development of Cushing’s syndrome, of reduction in the peripheral eosinophil leucocyte count, and of changes in urinary 17-ketosteroid excretion in patients receiving large doses of salicylates, while work on experimental animals confirmed that salicylates had certain cortisone-like properties.

However, it is probable that these effects of salicylates result from a purely non-specific stimulation of the pituitary-adrenal axis, since many other substances (collectively described by Selye as “non-specific stressor agents” and including ephedrine, colchicine, atropine, urethane, nitrogen mustards, and others) have a similar action, although most of them are completely ineffective in the treatment of the rheumatic diseases. Sodium salicylate must therefore have a specific anti-rheumatic action in addition to any such non-specific effect on the endocrine glands.

This thesis is supported by the results of experiments carried out by the authors at the Rheumatological Clinic of the Faculty of Medicine of Paris. It was confirmed that sodium salicylate has a direct corticotrophic action, but this was shown to be far too feeble to be responsible for its therapeutic efficacy, the depletion of adrenal ascobic acid caused by clinically effective doses of salicylate being far less than that resulting from therapeutically effective doses of ACTH. Again, whereas quite small doses of ACTH or cortisone definitely increased urinary corticosteroid excretion in five healthy subjects, large doses of sodium salicylate had no demonstrable effect. It must thus be concluded that, although sodium salicylate has an undoubted stimulant action on the pituitary-adrenal axis, the mechanism by which it exerts its specific therapeutic effect remains unknown.

Adrian V. Adams.


When rats weighing 80 to 100 g. are given daily injections of approximately 2 mg. cortisone they develop adrenal atrophy in 8 to 10 days—as after hypophysectomy. If, however, a similar quantity of testosterone is given together with the cortisone, the atrophy is prevented. Adrenal atrophy after prolonged cortisone administration is not unknown in human subjects, and several cases have been reported in which the condition has been fully confirmed post mortem. Fortunately, warning of the development of this atrophy can be obtained in the live patient by means of Thorn’s test (which was used in this study to evaluate the effect of testosterone) and the cortisone omitted, if necessary, in order to allow the adrenal cortex to recover. It has been customary to give ACTH (corticotrophin) for a period in such cases before reverting again to cortisone; in the opinion of the authors this is unnecessary if testosterone (acetate or propionate) is given at intervals during the administration of cortisone. The quantity they used in a series of cases described here was small (25 mg. weekly); it caused no side-effects and was equally efficacious in both men and women.

The patients were divided into four groups:

1. Six patients were treated with cortisone alone, and Thorn’s test revealed adrenal insufficiency in five after only 1-5 g. cortisone had been given;

2. Twelve patients received cortisone plus testosterone, and in half the cases adrenal function appeared to be unaffected;

3. Five patients who had been treated with cortisone alone and showed suppression of adrenal function were now given testosterone with cortisone, and it was found that in three of them normal function was restored;

4. Two patients had been receiving both hormones; testosterone was omitted and cortisone continued alone, Thorn’s test subsequently indicating adrenal damage.

The evidence suggests that testosterone exerts a protective effect. There is some evidence, also, that it counteracts the electrolyte disturbances caused by cortisone. The number of cases treated is small but the results obtained are sufficiently promising to justify more extensive trials.

D. Preiskel.


A number of workers in recent years have been concerned with the influence of ACTH (corticotrophin) and cortisone on antibody production in experimental animals. The present authors, continuing their studies on plasma-cell development during antibody formation, now describe the results of their investigation, carried out at the University of Zurich, of the influence of ACTH and cortisone on these responses in the rabbit. Previously, they had shown that antibody formation could be related to plasma-cell response in the spleen of rabbits and, in common with other workers, that administration of ACTH and cortisone could depress the formation of antibody in rabbits undergoing immunization against certain antigens. The present experiments were planned to obtain more detailed information about the effect of these substances on the antibody and plasma-cell response of rabbits, the immunizing agent used being a polyvalent typhoid-paratyphoid vaccine. (This was presumably of the heat-killed phenol-preserved type, since the antibody response was measured by the paratyphoid BH serum agglutinin titre. Precise details of the agglutination technique are not given, nor do the authors state whether the agglutinable suspension used for the test was a standardized monophasic suspension or a simple diphasic killed broth culture.)

The animals were first sensitized with an injection of the polyvalent vaccine, and after irregular intervals (generally about 3 weeks) they were re-injected with the vaccine, given intravenously. The treated animals received either cortisone or ACTH for varying periods and at different intervals in relation to the re-injected vaccine in the several series of experiments. Blood tests were made before re-injection, and finally the animals...
were bled out at different stated intervals, killed, and plasma-cell counts carried out on spleen smears; the same procedure was followed in the control animals, and the agglutinin response and plasma-cell counts were compared in the two groups.

In general, the authors showed that ACTH or cortisone, given either 2 hours or 10 minutes before, or simultaneously with, the intravenous re-injection of the vaccine, had little or no effect on the antibody or plasma-cell response. When, however, the hormones were given 7 days before the re-injection of the vaccine, there was a marked decrease in antibody production, and also a reduction in the absolute number of plasma cells in the spleen. [These findings are shown in two series of graphs, but it is difficult to follow the detailed results as given in various Tables.]

H. J. Bensted.


Although there have been many reports of the clinical effects of Filatov's tissue therapy, there have been few histochemical studies. In this study, carried out in the Department of Pathological Anatomy, Hôpital Bouchaout, Paris, two groups of male white rats received implants of an inert material ("sponge") under the muscular wall of the abdomen, the second group being given in addition three injections of 25 mg. cortisone in the course of one week; in a third group of animals the implant consisted of dried placenta. One animal from each group was then killed each week and the implants were investigated macroscopically and microscopically, specific stains for collagen, reticulin, amyloid, mucoid, and mucopolysaccharides being employed. The testicles and adrenal glands were also examined.

There was no hard fibrous tissue around the implant in the animals given cortisone, or in the group receiving the implant of placenta tissue, the two groups differing only in that the placental implants produced more blood vessels and, histochemically, a high concentration of mucopolysaccharides. In the cortisone-treated group the adrenal glands showed cortical atrophy, but in none of the three groups was there a change in the testicles. The authors suggest that placental tissue contains a principle which activates the proliferation of fibroblasts.

H. Lehmann.


The inter-relationship of adrenal function and vitamin-C metabolism was studied in a series of experiments carried out in the Dunn Nutritional Laboratory, Cambridge, in which an intramuscular injection of 2 mg. ACTH was given to guinea-pigs four times a day. These animals were not hypophysectomized.

Although the concentration of ascorbic acid in the liver and adrenal glands was diminished, the total quantity present was not affected, since the organs themselves became enlarged. Administration of ACTH did not hasten the onset of scurvy in guinea-pigs given a diet deficient in ascorbic acid, nor did it increase the rate of depletion of ascorbic acid from the liver or the adrenal glands during the development of deficiency. After a single injection of ACTH no substantial change was observed in the relative proportion of dehydroascorbic acid to ascorbic acid in the adrenal glands, although the concentration of ascorbic acid was seen to be temporarily depressed.

There was a remarkable increase in the weight of the liver in animals given ACTH; this was apparent after 2 days, and after 14 days amounted in young guineapigs to about 50 per cent. above the liver weight of control animals, and in adult guinea-pigs to an average of 39 per cent. During the first day or so the increase in the weight of the liver was due to extra glycogen and water, but thereafter there was an appreciable addition of protein. The size of the liver cells increased in proportion to the total increase in weight of the organ, as a result of an increased volume of the cytoplasm.

Administration of ACTH caused the percentage of fat in the liver to fall, but it had little effect on the concentration of sulphhydryl compounds. The absolute amount of water, glycogen, and protein continued to increase when the injections of ACTH were continued for periods up to 40 days, although there was some increase in the percentage of glycogen and some decrease in that of protein and fat, as compared with the controls. When administration of ACTH ceased the weight of the liver fell sharply, being about the same as that of controls after 2 days, and about 10 per cent. lower than that of controls after 3 to 30 days. The glycogen content fell to within normal limits within 2 days and the protein content fell likewise some days later.

Cortisone had a similar but more intense effect on the liver of young guinea-pigs, but there was no significant change in the average weight of any other organ except the kidneys, the weight of which increased from 8 to 20 per cent., according to the dose.

Similar effects were observed in rabbits, but not in young rats, mice, or chicks. Robert de Mowbray.


At the University of California Medical Center the opportunity was taken to investigate the effect of prolonged administration of adrenaline in five male patients who had been taking adrenaline regularly by subcutaneous injection for considerable periods for asthma, the object being to determine whether there was any evidence of sustained adrenal stimulation of the hypothalamus-adrenal-pituitary system, or if after a time this...
Surgery of the Adrenal Gland for Cushing's Syndrome.


It is now generally accepted that all patients with Cushing's syndrome have hyperadrenocorticism, with excess of 11-oxy-steroids. In some cases the condition is due to a tumour of the adrenal gland but more often to hyperfunction of the adrenal cortex, with or without hyperplasia. The stimulus causing the hyperadreno-corticism is not understood and it is only rarely that a basophilic pituitary tumour can be demonstrated. The excess of 11-oxy-steroids produces the characteristic signs of Cushing's syndrome. If there is excess of steroid metabolites resembling androgens the androgenic syndrome and Cushing's syndrome may be found in the same individual. Cushing's syndrome is twice as common in women as in men. The average age of onset is 30, and the span of life is shortened, although occasionally spontaneous remission does occur.

In this paper the results of treatment of 28 cases of Cushing's syndrome are presented from the Cleveland Clinic, Ohio. Of these, two were found to have a malignant tumour of the adrenal cortex, four a benign solitary adenoma of the adrenal gland, two solitary benign adenomas in hyperplastic glands, and the remaining twenty no tumour. Methods of diagnosis are discussed.

Treatment consists either of excision of any existing tumour or subtotal adrenalectomy in which all of one adrenal gland and 90 per cent. of the other is removed in a one-stage operation. At present it is not considered necessary to perform bilateral total adrenalectomy unless the disease is progressive following subtotal adrenalectomy and presents a threat to life. Simultaneous bilateral inspection of the adrenals is advised before any definitive operative procedure on the glands is performed. If both glands appear atrophic search must be made for a cortical adenoma in an aberrant situation, accessory adrenal tissue being present in 20 per cent. of all individuals.

The use of cortisone and other hormones in replacement therapy is discussed. Operation has been made safer by the preoperative administration of cortisone, which is continued in decreasing doses after operation, or it may have to be continued indefinitely if the remaining adrenal fragment is incompetent. ACTH may be used to stimulate an atrophic gland, and deoxycorticosterone acetate (DOCA) may also be necessary after operation. With adequate resection of the adrenals almost all the abnormal features disappear, although osteoporosis, which is often present, is late in responding. Hypertension, possibly due to irreversible changes in the arteries, is sometimes uninfluenced by operation and serious vascular disease may occur at an early age in Cushing's syndrome in spite of adequate therapy.

In a group of eight patients operated on since cortisone became available there were no operation deaths. One died 9 months after operation from perforated duodenal ulcer, another required a second operation for total adrenalectomy, but the other six are well.

In an earlier group of twelve patients one died; in five undergoing bilateral hemi-adrenalectomy three are well, one is improved, and one died of adrenal failure.

Of five patients undergoing operative investigation only, three who were traced had all died of complications of Cushing's syndrome.

W. Skyrme Rees.


Among laboratory aids to the diagnosis of adrenocortical insufficiency Kepler's test is considered the most useful, but it is complicated and tedious to perform. Soffer and Gabrilove (Metabolism, 1952, 1, 504) have proposed a simplified version of this test, but it is said to have the disadvantage that often the patient is unable to ingest the necessary quantity of water (1,500 ml) without vomiting and that each of the two parts of the test lasts 5 hours. The present author now describes a modification of these tests which he claims is simpler to perform and more specific in its results.

Following overnight deprivation of fluid, the patient is asked to drink as much water as possible up to a total of 1 litre in 20 minutes. The urine flow is then measured at intervals of 15 to 20 minutes for 2½ hours. The maximum rate of urine flow in adrenocortical insufficiency is low—less than 2 to 3 ml per minute.) The test is repeated next day 4 hours after the oral administration of 50 to 75 mg cortisone.

In performing this test it is necessary to observe the following precautions:

1) The patient's serum sodium level must not be very low, because then even the administration of cortisone will fail to produce a normal diuresis;
2) The dose of cortisone must not be less than 50 mg;
3) The control and test observations must be made at the same time of the day;
4) The water should be drunk when the cortisone activity is at its highest level as measured by eosinophil depression (4 to 8 hours after ingestion in adrenal insufficiency).

The author gives reasons for regarding this test as better than other excretory tests and discusses its use in differential diagnosis.

Norval Taylor.

The authors present experimental evidence to show that the effect of a subcutaneous injection of ACTH (corticotrophin) on the adrenal cortex of the rat is enhanced by its administration in a medium which delays absorption of the hormone. Hypophysectomized Sprague-Dawley male rats of 110 to 115 g. body weight were used, each group being given a subcutaneous injection of 1 U.S.P. unit ACTH dissolved in 0.5 ml. of one of the following test solutions:

- 0.2 per cent. suramin,
- 5 per cent. phosphorylated hesperidin,
- 2.5 per cent. phosphorylated hesperidin,
- 5 per cent. hesperidin methyl chalcone,
- 15 per cent. gelatin,
- 15 per cent. gelatin plus 20 T.U. hyaluronidase,
- 15 per cent. gelatin plus 4 per cent. phosphorylated hesperidin.

Control animals received injections of the test solutions without ACTH. In each group the ascorbic acid content of the left adrenal gland was determined by the method of Mindlin and Butler 3 hours after the injection, and that of the right gland 6 hours after the injection, the effect of the ACTH being judged from the degree of depletion of adrenal ascorbic acid found.

Of the single agents tested, the most effective in enhancing the action of ACTH were phosphorylated hesperidin and heavy gelatin, while a combination of these two substances was even more effective, the maximum response being greater than with either agent alone and its appearance being delayed until the 6th hour. The possible mechanism of this delay of absorption was investigated in vitro, and the activity of phosphorylated hesperidin and hesperidin methyl chalcone in inhibiting the tryptic digestion of casein, as determined by the method of Anson (J. gen. Physiol., 1938, 22, 79), was shown to be similar in degree. It was therefore concluded that the delaying action of the former was due not to its antiproteolytic properties, but to its inhibiting effect on tissue hyaluronidase, the methyl chalcone of hesperidin having no such action. It is suggested, however, that the greater effectiveness of the combination of gelatin with phosphorylated hesperidin may be due to the antiproteolytic properties of the latter, the tissue proteinases being prevented from acting on the gelatin, which thus retains its depot effect for a longer period of time and reinforces the antihyaluronidase action of the phosphorylated hesperidin.

D. G. Adamson.


It has been observed that the increased protein catabolism following injury such as fracture, strikingly resembles the effects of administration of adrenocorticotrophic hormone or cortisone. In the present investigation, carried out at the Rowett Research Institute, Aberdeen, the results in these two events were compared, using rats as the experimental subjects. Male rats weighing 300 g. and maintained on a constant food intake were divided into four groups of six animals each, and treated in one of the following ways:

1. subcutaneous implantation of 25 mg. cortisone acetate;
2. fracture of the femur by open operation;
3. subcutaneous implantation of 50 mg. cortisone acetate;
4. fracture of femur plus implantation of 25 mg. cortisone acetate subcutaneously.

A control group was treated by sham operation and showed little disturbance of nitrogen metabolism.

Estimation of the urinary nitrogen output in the test animals showed that the effect of fracture was similar in character and magnitude to that of implanting a 25-mg. pellet of cortisone acetate. The result of adding a second 25-mg. pellet through the same incision was similar to that of simultaneous fracture and implantation of one pellet; in both cases the effect was greater than for one event only, but not as great as if they were additive. These observations suggest that the effect of fracture on the femur in the rat is roughly equivalent to the effect of the slow liberation of 25 mg. cortisone from the adrenal cortex, and that increasing the stimulus (as measured by cortisone) increases the response. It is not considered justifiable at present, however, to conclude from this that any such injury would cause the liberation of such a quantity of glucocorticoid from the adrenal cortex.

Nancy Gough.


In this paper from the Mayo Clinic two cases are described in which, after prolonged administration of cortisone for rheumatoid arthritis, the patients died from irreversible shock after a major surgical operation.

The first patient was a woman of 54 years, who had received cortisone for one year before admission in a dosage of 75 mg. three times a week, increased after 4 months to 100 mg. a day. Symptoms of gastric ulceration developed, and 7 days after admission a haematemesis occurred. A partial gastrectomy was performed, but the patient did not regain full consciousness; signs of shock developed, and she died, despite emergency measures which included administration of 300 mg. cortisone.

The second patient, also a woman of 54 years, had received a prolonged course of both cortisone and ACTH for rheumatoid arthritis. During this treatment she developed moon-face. Administration of cortisone was discontinued when the patient was admitted to hospital for treatment of the rheumatoid arthritis, but intravenous arterial injections of hydrocortisone to a total of 422 mg. were given in the 41 months before bilateral bunionsectomy was performed, the last injection being given 2 weeks before the operation. The patient withstood the operation well, but 15 hours afterwards shock developed which did not respond to cortisone and intravenous injection of hydrocortisone.
In both patients the basophilic cells of the anterior pituitary showed loss of granulation, vacuolization, and hyalinization, while the adrenal cortex was considerably decreased in thickness, owing to a diminished number of cells rather than to diminished cellular size. There was lack of lipoid material in the zona glomerulosa and zona fasciculata, with congestion of the zona reticularis.

The authors also examined the adrenal glands of adult patients who had died from various disease conditions for which they had received cortisone. It was found that there was often a decrease in the size of the glands, that though the total adrenal weight might be normal there could be quite marked histological changes, and that after cortisone has been discontinued for an interval of several weeks or more, signs of recovery were apparent. It is pointed out that these changes are secondary to depression of endogenous ACTH, and that the same situation, with the same hazards, might arise after prolonged treatment with this hormone.

In the authors' view, a patient who has received intensive ACTH or cortisone therapy with a period of 6 to 12 months before operation, particularly if there are signs of hypercorticism, should be regarded as having deficient reserve adrenocortical function. Intramuscular injections of 200 mg. cortisone should be given 48, 24, and 1 to 2 hours before operation, with a gradual tailing off of the drug during the subsequent 3 to 4 days. The patient should not receive intravenous infusion of glucose solution without sodium chloride, and morphine, which is also a special hazard in patients with deficient adrenocortical function, should be avoided.

G. A. Smart.


The results are reported of a series of clinical and laboratory investigations which have been carried out at the Rheumatology Centre of the University of Rome into the antirheumatic activity of colchicine and the effect of the drug on pituitary and adrenocortical function. The chief findings were as follows:

Colchicine did not appear to increase the therapeutic action of cortisone in rheumatoid arthritis;
the improvement noted in ten patients who received 50 mg. cortisone intramuscularly and 1 to 2 mg. colchicine by mouth daily for 20 days showed no appreciable difference from that observed in ten comparable cases treated with cortisone only in the same dosage.
A single dose of 2 mg. colchicine by mouth to rheumatic subjects diminished the number of circulating eosinophils by an average of 13-2 per cent.
The same dose given daily increased the urinary excretion of 11-oxy steroids by an average of 39 per cent., suggesting that the drug has some adrenocorticotropic effect.

In some experiments in animals it was found that colchicine reduced the spreading effect and suppressed some of the histological effects of hyaluronidase injected intradermally. After repeated administration of colchicine to guinea-pigs for 3 to 7 days, histological examination showed evidence of over-activity in the zona fasciculata and zona glomerulosa of the adrenal cortex, an increase in the eosinophil cells of the pituitary gland, and involution of lymphoid tissue, while after 10 days the liver showed vacuolization and glycogen infiltration, the appearances being similar to those found after the administration of cortisone. There were no changes in the pancreas, however, in contrast to the findings after cortisone administration. Colchicine was also shown to cause degenerative changes in the muscle fibres of the heart.

It is concluded that, despite its lack of short-term antirheumatic effect, colchicine has a definite ACTH-like action. Its clinical use over a long period is precluded by its toxic effects.

V. C. Medvei.


In three patients suffering from arthritis, for which treatment with ACTH and cortisone was given at the Södersjukhuset, Stockholm, changes in the blood and bone marrow were observed. There was stimulation of erythropoiesis and of the formation of polymorphonuclear leucocytes, but not of lymphocytes. Treatment with ACTH, and to a lesser degree with cortisone, produced eosinopenia. The observations were not quite constant, and this the authors consider was due to the fact that the three patients received different dosages of the hormones. They are unable to say if the finding that cortisone had a less profound effect than ACTH on the bone marrow and peripheral blood picture was due to an essential difference between the action of the two drugs, or whether it was because ACTH was given in a higher dosage.

H. Lehmann.

Haematological Changes in the Bone Marrow and Peripheral Circulation due to Treatment with Cortisone and ACTH. (Modificazioni del quadro ematologico (midollare e periferico) in corso di cura con cortisone e ACTH.) Scalabrino, R., Curtarelli, G., and Bombelli, R. (1952). Haematologica, 36, 823. 16 figs., bibl.

At a Milan hospital careful serial examinations of the blood picture were made on a series of 32 patients with a variety of acute, subacute, and chronic rheumatic conditions, including a number with carditis, and certain other diseases, all of whom were treated with cortisone or ACTH for variable periods and with a variable dosage.

In nineteen patients the total leucocyte count increased and in eleven it decreased. The lymphocyte count decreased in the majority of patients, although this decrease was not constant and did not always persist, and in the spleen and lymph nodes the lymphoid centres became less marked and less cellular when the hormones were given in large doses. The neutrophil granulocyte count increased in almost all cases, and that of eosinophil granulocytes decreased in most, but only temporarily.
In the bone marrow the number of eosinophil cells showed no changes with treatment. A slight rise in the reticuloocyte count occurred in eleven patients, and the haemoglobin content and erythrocyte count increased slightly—partly as a result of treatment, but possibly owing to a natural remission of the disease process in some cases.

E. Neurmark.


At the University of Zürich the effect of ACTH (corticotrophin) and cortisone on the phagocytic activity of the leucocytes and the macrophages of rabbits was investigated.

Macrophages were obtained from a pleural exudate induced by the intrapleural injection of broth and gum arabic; the exudate was mixed with suspensions of Staphylococcus aureus and the number of cells containing ingested bacteria estimated after 30 minutes. ACTH or cortisone added in vitro had no effect on phagocytosis, but when either drug had been given to the animals for a week or more before the experiment there was slight but distinct inhibition, becoming more marked as the period of administration was increased. This result is attributed to a reduction in the production of macrophages and in the potency of chemotactic factors. In the blood of animals treated with cortisone, however, no inhibition of phagocytosis by the leucocytes could be demonstrated.

E. Neurmark.

Thymus Involution Test for ACTH. [In English.] THING, E. (1953). Acta endocr. (Kbh.), 13, 343. 4 figs, 7 refs.

The usual method used for the assay of ACTH (corticotrophin), the ascorbic acid depletion test, suffers from the disadvantage that it requires hypophysectomized animals. A method involving the use of intact animals, based on an observation by Hayashida and Li (Endocrinology, 1952, 50, 187) that the weight of the thymus decreases under the influence of ACTH in normal 21-day-old rats, has been described by Bruce and others (Lancet, 1952, 1, 790), and has been further investigated by the present author, 1,500 nesting rats 7 to 10 days old being used. Since the thymus requires a constant stimulus, the ACTH was administered in an oily medium consisting of arachis oil with 5 per cent. beeswax. Injections were given once daily for 3 days, and 24 hours later the thymus was removed and weighed. From the average results obtained with different doses, dose-response curves were constructed. The oily medium alone was without effect on the thymus, and stress substances such as formalin had to be administered in very large amounts before more than slight involution occurred, whereas it was confirmed that a quantitative relation existed between the dose of ACTH administered and the degree of thymus involution produced. The reliability of the tests seemed to be equal to that of established methods, but its sensitivity was less, the amount of active material necessary to produce a significant response being about ten times greater than in the ascorbic acid depletion test.

Nancy Gough.


ACTH (corticotrophin) in oil-beeswax suspension was administered to adult hypophysectomized rats to investigate its ability to produce adrenal hypertrophy and thymus involution. The study was begun 14 days after hypophysectomy and the 155 rats were divided into three groups, the first being given ACTH in aqueous solution, and the second ACTH in arachis oil with 5 per cent. beeswax, the third being used as controls. The ACTH was given at various dosage levels (five animals per dose), and the doses given in aqueous solution being ten times greater than those given in oily suspension. The degrees of thymus involution and adrenal hypertrophy found after 3 days' treatment were about equal in both groups, indicating that one dose of the slowly-absorbed ACTH preparation is equal in effect to ten doses of aqueous ACTH. Nevertheless, the amount of hormone required to obtain a measurable response was ten times greater than that required when intact nesting rats were used, and the author therefore concludes that the method of assay of ACTH by determination of its effect on the adrenal weight and thymus involution in adult hypophysectomized rats is of no practical value.

Nancy Gough.


The relationship, if any, between a rise or fall in the eosinophil count and the clinical changes in patients receiving cortisone or ACTH was studied at Queen Mary Veterans' Hospital, Montreal. In 35 of 56 patients, most of whom were suffering from bronchial asthma or rheumatoid arthritis, there was a fall in the eosinophil count of at least 50 per cent. after administration of cortisone, but no parallel was observed between this fall and the efficacy of the treatment. In twenty of these 35 patients the eosinophil count rose later during treatment ("escape" of the eosinophils), but once again this did not parallel an improvement or deterioration in the clinical condition. In the authors' view ACTH is a stronger eosinopenic agent than cortisone [this view, however, is based on the results in only two cases, in which a course of ACTH was given after a course of cortisone.] They state that if two courses of cortisone are given the fall in the eosinophil count is less during the second course [but this finding is based on three cases only, in one of which the second course was given after an interval of one year]. The authors found wide variations in the eosinophil count in the same patient, even when it was determined at the same time each day. [These variations, which have been noted by many other workers, do not...


Other General Subjects


In this iconoclastic essay the author examines the career of Baron Dupuytren and concludes that historians have continued to accept this “celebrated” French surgeon at his own valuation without real justification.
The many faults in his personal character have long been admitted; in addition, the author cites the numerous achievements of Dupuytren's contemporaries in one of the most brilliant periods of French medicine and shows how Dupuytren, through ignorance or jealousy, did his best to minimize or deny their importance. The most striking examples of this harmful egomania are his treatment of Louyer-Villermay's account of appendicitis (1824), owing to which it is still not appreciated that this work anticipated that of Fitz; and—more important—the extraordinary history of "Lembert's suture". The author states that this epoch-making advance in intestinal surgery was really carried out by Charles Lambert, a pupil of Dupuytren's hated rival, Lisfranc, and was reported to the Académie Royale de Médecine on January 26, 1826. Dupuytren later attributed it to his own pupil, Antoine Lembert, and said that even Lembert had been anticipated by another of his pupils, Jobert de Lomballe ("both are equally perfect"). In fact, the latter had merely repeated methods used in the 17th and 18th centuries by Palpyn and Ledran and had taken them no farther.

[Those who wish to investigate this claim are referred to the author's history of intestinal suture (Rassegna Clinico-Scientifica, 1947, 23, 84.)]

[Without accepting all the author's conclusions, it must be admitted that he has presented a strong case for a critical reassessment of Dupuytren's role in the history of surgery.] F. N. L. Poynter.


The authors review the somewhat contradictory literature on the results achieved by massage with a cream containing adrenaline in the treatment of patients suffering from rheumatic conditions. Their own trial at the Walkden Miners' Clinic and Rheumatism Research Centre, Manchester University, embraced investigation both of the efficiency of adrenaline cream as a pain-reliever and of the recovery times of patients under treatment. In one investigation 65 patients were treated, approximately one-half of them with adrenaline cream and one-half with a similar cream containing no adrenaline. At the time of treatment neither the doctors nor the physiotherapists knew which cream they were using. In another investigation sixty patients were treated with adrenaline cream, by dry massage, and without massage for three consecutive periods, but the order in which the treatments was carried out varied, and other physiotherapeutic measures, such as heat treatment, were applied without interruption. Results were assessed on the basis of whether relief from pain was complete, partial, or non-existent. It was found that dry massage gave more relief than massage with simple cream, and that massage with adrenaline cream "produced complete relief in a significantly greater proportion of patients than simple cream". It was concluded that massage with adrenaline cream and dry massage produced a similar degree of palliation.

Another investigation was carried out to ascertain the effect of adrenaline cream on recovery, 64 alternate patients being treated with either adrenaline cream or simple cream until complete relief was obtained or no further improvement could be expected. While the final results achieved in the two groups were the same, it was found that there was a significant difference in the time taken to return to work between the two groups: all those in the group treated with simple cream returned to work by the end of the investigation, but of those treated with adrenaline cream three failed to return to work and two who were originally at work had to stop.

Discussing their findings, the authors point out that the mode of action of adrenaline cream is by no means clear, but they suggest that the delay in recovery following the use of this substance may be due to an interference with the pain-defence mechanism. W. Tegner.


The blind spot may be enlarged in the vertical meridian, and so point to changes in the blood vessels of the optic nerve. As part of the affection of the vascular system, the retinal vessels may be involved, producing a concentric narrowing of the field of vision. It is possible that some hardly noticeable scieritis, especially on the posterior segment of the eyeball, may lead to myopia. The nutrition of the sclera may be affected. N. Pines.


Leukergy in Diseases of the Locomotor Apparatus. (La leucergia in alcune malattie dell'apparato locomotore.) DANEO, V., and SECONDO, G. (1953). Reumatismo, 5, 313. 27 refs.